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European Implementation of Bacteriophage Therapy: Impact of Medicinal Product Legislation on Tailored Hospital Care

G. Verbeken, Biologist
Burn Wound Center,LabMCT
Human Cell- and Tissue Banks
Queen Astrid Military Hospital
Brussels, Belgium

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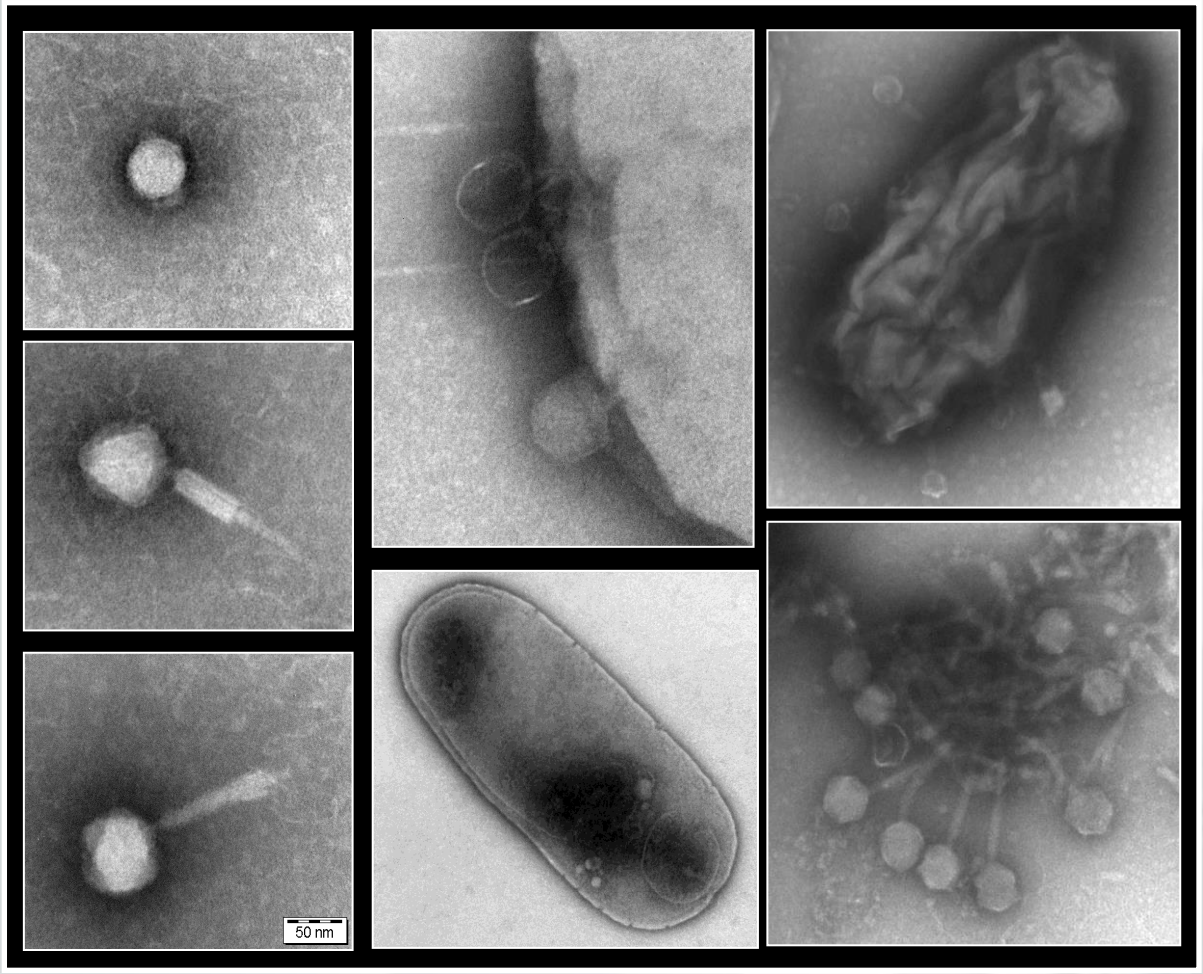
BFC 1



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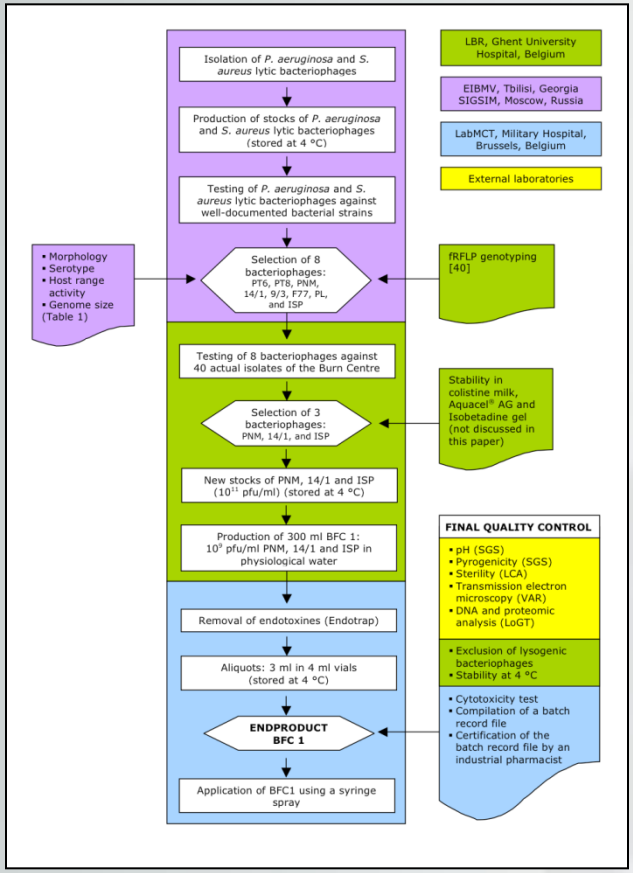
QC Phage Production



- Lack off well-defined, quality-controlled phage preparations
- Often inadequate matching of bacteria and phages (empirically)
- Endotoxins in crude phage preparations
- “GMP-like” (small scale) production

OPEN ACCESS Freely available online PLoS one

Quality-Controlled Small-Scale Production of a Well-Defined Bacteriophage Cocktail for Use in Human Clinical Trials

Maya Merabishvili[1,2,8], Jean-Paul Pirnay[2]*, Gilbert Verbeken[2], Nina Chanishvili[1], Marina Tediashvili[1], Nino Lashkhi[1], Thea Glonti[1], Victor Krylov[3], Jan Mast[4], Luc Van Parys[5], Rob Lavigne[6], Guido Volckaert[6], Wesley Mattheus[6], Gunther Verween[2], Peter De Corte[2], Thomas Rose[2], Serge Jennes[2], Martin Zizi[5,7], Daniel De Vos[2], Mario Vaneechoutte[8]

1 Eliava Institute of Bacteriophage, Microbiology and Virology (EIBMV), Tbilisi, Georgia, 2 Laboratory for Molecular and Cellular Technology (LabMCT), Burn Centre, Queen Astrid Military Hospital, Bruynstraat, Neder-over-Heembeek, Brussels, Belgium, 3 Laboratory of Bacteriophage Genetics, State Institute for Genetics and Selection of Industrial Microorganisms (SIGSIM), Moscow, Russia, 4 Unit Electron Microscopy, Veterinary and Agricultural Research Centre (VAR), Ukkel, Brussels, Belgium, 5 Section Health of the Division Well-Being (Belgian Defence Staff), Queen Astrid Military Hospital, Neder-over-Heembeek, Brussels, Belgium, 6 Laboratory of Gene Technology (LoGT), Katholieke Universiteit Leuven, Leuven, Belgium, 7 Department of Physiology (FYSP), Vrije Universiteit Brussel, Jette Brussels, Belgium, 8 Laboratory of Bacteriology Research (LBR), Ghent University Hospital, Ghent, Belgium

Study Launch 07/09/2007

Checklist mbt Experiment 2007/007

Mbt bacteriofaagcocktail BCF1.4

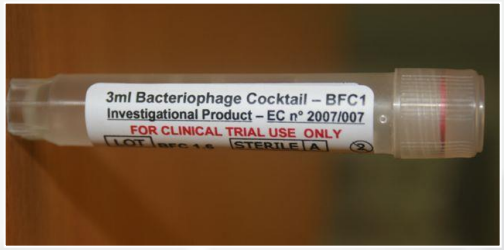
Cocktail bedoeld voor gebruik binnen klinische studie 2007/007

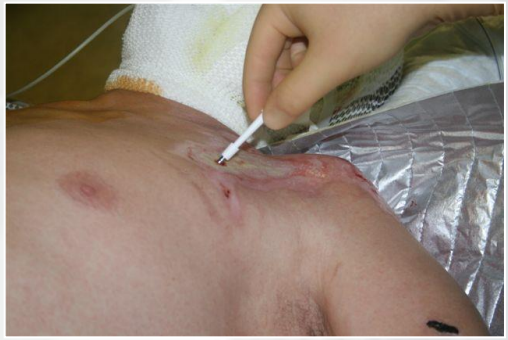
Protocol: VUB dd 01/09/2007

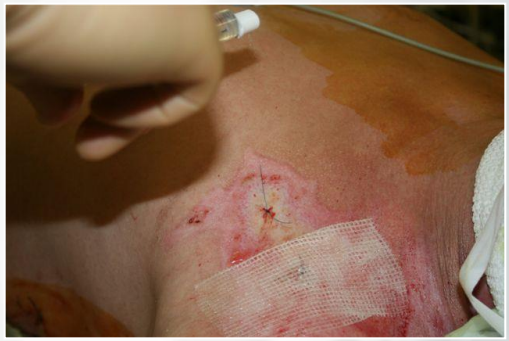
Studielokatie: Brandwondencentrum HCB-KA

Goedkeuring door Commissie Medische Ethiek	OK / 28 juni 2007 Ref. 2007/007 (UZ-Brussel)
Aanwezigheid foutloze studieverzekering	OK / 07 juni 2007 Ref. 45.147.458 (Ethias)
Aanwezigheid goedgekeurde patiënten - informatieformulieren (N/F)	OK / EC / 20 juni 2007
Aanwezigheid goedgekeurde patiënten - toestemming - formulieren (N/F)	OK / EC / 20 juni 2007
Certificatie BFC1.4 door industrieapotheker	OK / Apth. L. Van Parijs / Erkenning 1484
Notificatie studie aan FOD Volksgezondheid (FAGG, Dept. R& D) door Com. Med. ethiek	OK / 28 juni 2007
Notificatie aan Orde der geneesheren door "Coordinating Investigator"	OK / 08 sept. 2007
Amendement mbt correctie Diensthoofd en correctie Investigatorenopsomming doorgegeven aan Com. Med. Ethiek	OK / 03 sept. 2007
Aanwezigheid van door I.A. goedgekeurde Batch Record File (en de erin gerefereerde Working Instructions)	OK / LabMCT / Lokaal 1- 240
Aanwezigheid Case Report Form mbt studie	OK / LabMCT / Lokaal 1-249
Aanwezigheid CV Coordinating Investigator	OK / "T" LabMCT / Folder "CVs"
Organisatie investigatorenmeetings	OK / 27 juni 2007 en 9 aug. 2007
Aanwezigheidslijsten investigatorenmeetings	OK / Masterfile BFC1
Distributielijst "binder" aan studiebetrokkenen	OK / Masterfile BFC1

VERBEKEN GILBERT
LAB MCT
QA-QC/RA
7/9/2007







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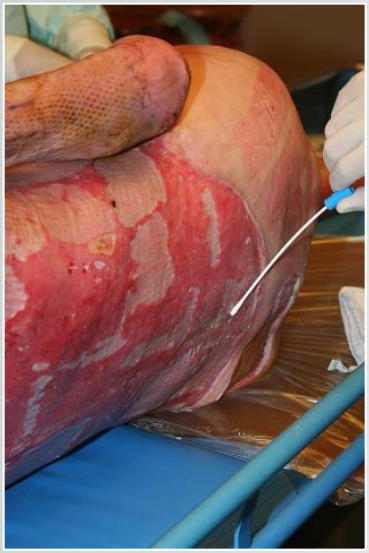
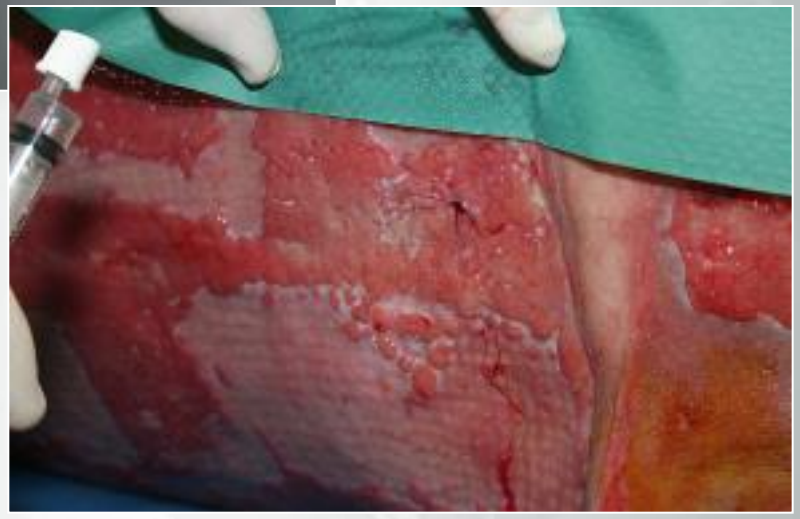
Patient Treatment





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Int J Burn Trauma 2014;4(2):66-73
www.IJBT.org /ISSN:2160-2026/IJBT0001948

Original Article

Experimental phage therapy of burn wound infection: difficult first steps

Thomas Rose[1], Gilbert Verbeken[2], Daniel De Vos[2], Maya Merabishvili[2,3,4], Mario Vaneechoutte[4], Rob Lavigne[5], Serge Jennes[1], Martin Zizi[6], Jean-Paul Pirnay[1]

[1]Burn Wound Center, Queen Astrid Military Hospital, Bruynstraat 1, B-1120 Brussel, Belgium; [2]Laboratory for Molecular and Cellular Technology, Burn Wound Center, Queen Astrid Military Hospital, Bruynstraat 1, B-1120 Brussel, Belgium; [3]Eliava Institute of Bacteriophage, Microbiology and Virology, 3, Gotua street, Tbilisi 0160, Georgia; [4]Laboratory of Bacteriology Research, University of Ghent, De Pintelaan 185, B-9000 Gent, Belgium; [5]Laboratory of Gene Technology, Katholieke Universiteit Leuven, Kasteelpark Arenberg 21, B-3001 Leuven, Belgium; [6]Department of Physiology, Vrije Universiteit Brussel, Laerbeeklaan 101, B-1090 Brussel, Belgium

Received August 18, 2014; Accepted September 8, 2014; Epub October 26, 2014; Published October 30, 2014

Int J Burn Trauma October 2014

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

35.

In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

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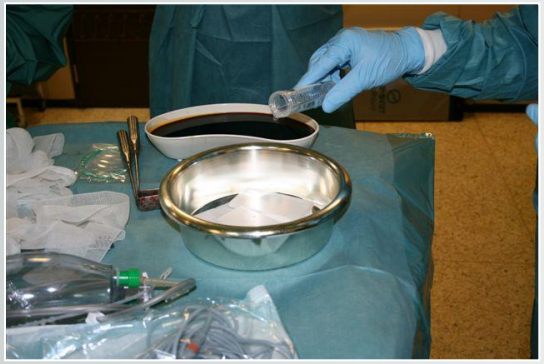
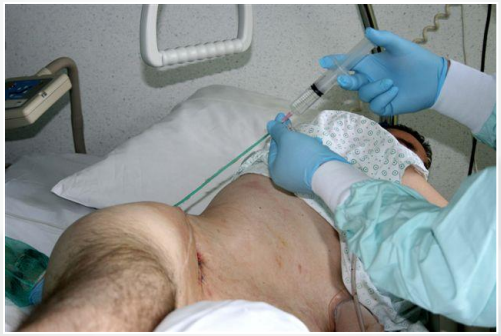
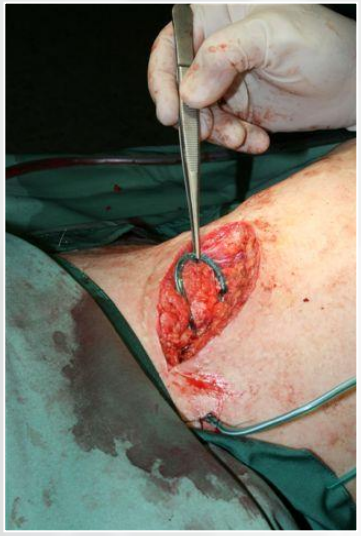
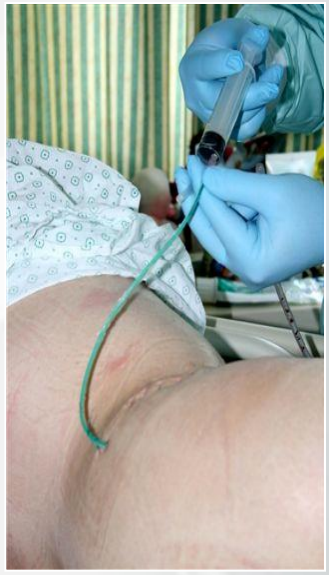
Declaration of Helsinki









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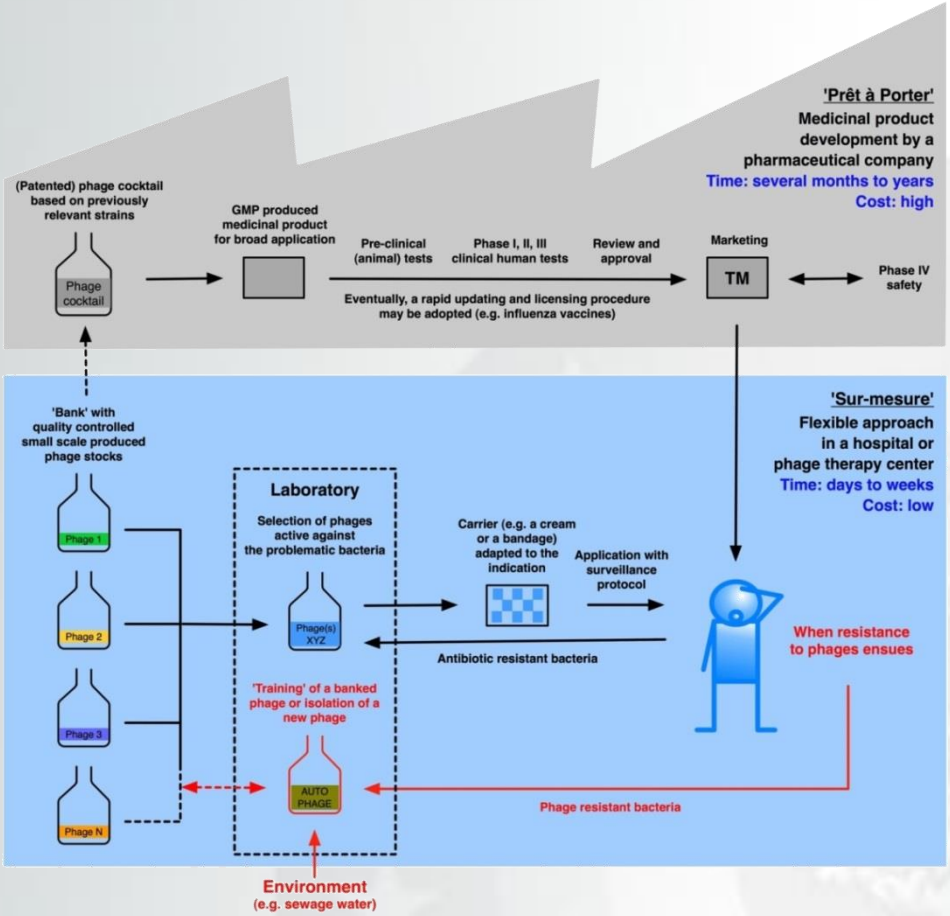
‘Prêt-à-porter’ vs ‘Sur-mesure’



The *evolutionary bacterial-phage dynamics* can only be put to full advantage in therapy *when using a timely and flexible approach*

ANNEX 1 Directive 2001/83/EC (Medicinal Products for Human Use)

Part I: Standardized marketing authorisation dossier

Part II: Specific marketing authorisation dossier

- Well-established medicinal use
- Essentially similar medicinal products
- Additional data required in specific situations
- Similar biological medicinal products
- Fixed combination medicinal products
- Documentation for applications in exceptional circumstances
- Mixed marketing authorisation applications

Part III: Particular medicinal products

- Biological medicinal products < Bacteriophage Therapy M.P.
  - Plasma-derived medicinal products
  - Vaccines
- Radio-pharmaceuticals and precursors
  - Radio-pharmaceuticals
  - Radio-pharmaceutical precursors for radio-labelling purposes
- Homeopathic medicinal products
- Herbal medicinal products
- Orphan medicinal products

Part IV: Advanced Therapy Medicinal Products

- Gene therapy medicinal products
- Somatic cell therapy medicinal products
- Tissue engineered products
- Combined advanced therapy medicinal products

East vs. West

WEST

Frederic Twort
UK 1915

Felix d'Hérelle
France/Canada 1917

"User-friendly" ANTIBIOTICS
1940s - Today

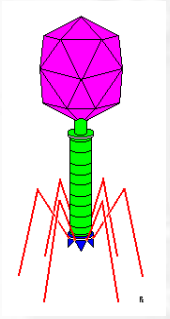
Antibiotic resistance
BWC/QAMH

Stalin WW II

EAST

George Eliava
Georgia, USSR

Eliava Institute, Tbilisi,
Georgia 1923 - Today



Phages

Dr. Maya Merabishvili

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The past …

- Eli Lilly and Company
- Swan Myers (Abbot Laboratories)
- Squibb and sons (B. M. S.)
- Laboratoire Parke-Davis (Pfizer)
- Instituts Pasteur de Paris et de Lyon
- Laboratoire du Bactériophage (5 prep.) (Robert & Carrière)
- German company Antipiol
- Saphal en Suisse
- Ex-URSS (Géorgie –Russie)

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Today: Phage applications in the Eliave Phage Therapy Centre, Tbilizi, Georgia

Institut George Eliava Tbilissi, Géorgie [B]

Laboratory of Phage Morphology and Biology, specialized on phage selection and creation of phage preparations

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For reprint orders, please contact:
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SPECIAL REPORT

European regulatory conundrum of phage therapy

Gilbert Verbeken,
Daniel De Vos†,
Mario Vaneechoutte,
Maya Merabishvili,
Martin Zizi &
Jean-Paul Pirnay

†Author for correspondence
Hospital Center of the Base – Queen Astrid, Laboratory for Molecular & Cellular Technology, Burn Unit

The treatment of infectious diseases with antibiotics is becoming increasingly challenging. Very few new antimicrobials are in the pharmaceutical industry pipeline. One of the potential alternatives for antibiotics is phage therapy. Major obstacles for the clinical application of bacteriophages are a false perception of viruses as 'enemies of life' and the lack of a specific frame for phage therapy in the current Medicinal Product Regulation. Short-term borderline solutions under the responsibility of a Medical Ethical Committee and/or under the umbrella of the Declaration of Helsinki are emerging. As a long-term solution, however, we suggest the creation of a specific section for phage therapy under the Advanced Therapy Medicinal Product Regulation.

Future Microbiology, October 2007

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Pharm Res
DOI 10.1007/s11095-010-0313-5

COMMENTARY

The Phage Therapy Paradigm: *Prêt-à-Porter* or *Sur-mesure*?

Jean-Paul Pirnay • Daniel De Vos • Gilbert Verbeken • Maia Merabishvili • Nina Chanishvili • Mario Vaneechoutte • Martin Zizi • Geert Laire • Rob Lavigne • Isabelle Huys • Guy Van den Mooter • Angus Buckling • Laurent Debarbieux • Flavie Pouillot • Joana Azeredo • Elisabeth Kutter • Alain Dublanchet • Andrzej Górski • Revaz Adamia

Received: 22 July 2010 / Accepted: 27 October 2010

Pharm Res, November 2010

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Arch. Immunol. Ther. Exp.
DOI 10.1007/s00005-012-0175-0

REVIEW

Optimizing the European Regulatory Framework for Sustainable Bacteriophage Therapy in Human Medicine

Gilbert Verbeken · Jean-Paul Pirnay · Daniel De Vos · Serge Jennes · Martin Zizi · Rob Lavigne · Minne Casteels · Isabelle Huys

Received: 3 January 2012 / Accepted: 21 February 2012

Arch. Immunol. Ther. Exp., April 2012

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Review
Future Virology

Introducing yesterday's phage therapy in today's medicine

Jean-Paul Pirnay*[1], Gilbert Verbeken[1], Thomas Rose[1], Serge Jennes[2], Martin Zizi[3,4], Isabelle Huys[5,6], Rob Lavigne[7], Maia Merabishvili[1,8,9], Mario Vaneechoutte[8], Angus Buckling[10] & Daniel De Vos[1]

[1]Laboratory for Molecular & Cellular Technology, Burn Wound Centre, Queen Astrid Military Hospital, Brussels, Belgium
[2]Burn Wound Centre, Queen Astrid Military Hospital, Brussels, Belgium
[3]Well Being Department, Queen Astrid Military Hospital, Brussels, Belgium
[4]Department of Physiology, Free University Brussels, Brussels, Belgium
[5]Department of Pharmaceutical & Pharmacological Sciences, Centre for Pharmaceutical Care & Pharmacoeconomics, KU Leuven, Leuven, Belgium
[6]Center for Intellectual Property Rights, KU Leuven, Leuven, Belgium
[7]Laboratory of Gene Technology, KU Leuven, Leuven, Belgium
[8]Laboratory of Bacteriology Research, Faculty of Medicine & Health Sciences, Ghent University, Ghent, Belgium
[9]Eliava Institute of Bacteriophage, Microbiology, & Virology, Tbilisi, Georgia
[10]Biosciences, University of Exeter, Cornwall Campus, Penryn, UK
*Author for correspondence: Tel.: +32 2 264 4844 ▪ Fax: +32 2 264 4907 ▪ jean-paul.pirnay@mil.be

Future Virology, April 2012

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Opening Remark ITF Meeting
July 12th 2011 / EMA London

Bacteriophage Therapy is a

Therapy Concept

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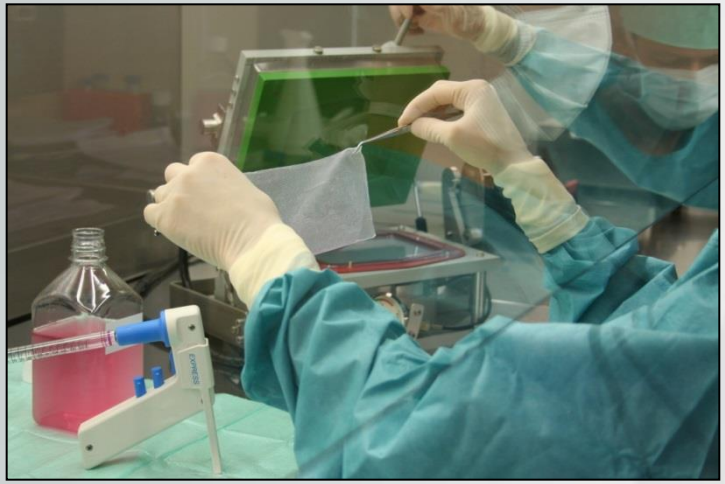
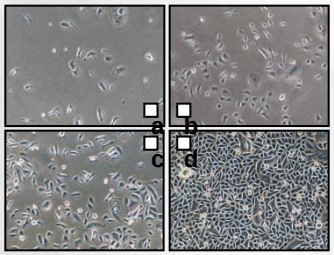
Accredited Human Keratinocyte Bank

R.I.Z.I.V. (I.N.A.M.I.) 7-19001-60-219



Grafting Keratinocytes Since 1987
More Than 1.000 Patients Treated

ISO 9001 CERTIFIED VINÇOTTE



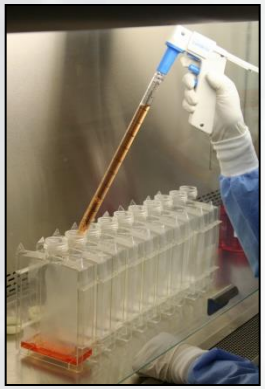
Donor Keratinocytes

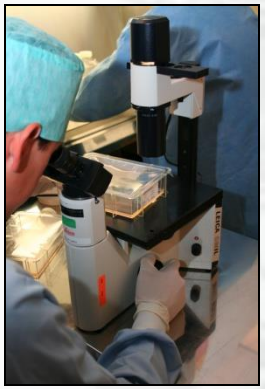
Donor Testing 02-006 (Testing Mother)

Test	Visit 1 (0-14 d after birth)	Visit 2 (6-8 m after birth)	Visit 3 (15 m after birth)
anti- HAV	Negative		
HBsAg	Negative		Negative
anti-HBs	Negative.		Negative
anti-HBc	Negative.		Negative
HBV-DNA (PCR)	Negative		
anti-HCV	Negative		Negative
HCV-RNA (PCR)	Negative		
anti-HIV	Negative		Negative
HIV-Ag	Negative		
HIV-RNA (PCR)	Negative		
anti- HTLV1&2	Negative		
TPHA	Negative		
anti-CMV IgG	Negative		
anti-CMV IgM	Negative	Negative	
anti-EBV IgG	Positive		
anti-EBV IgM	Negative		
GPT	Negative		

Master Cell Bank Testing 02-006

Test	MCB
Sterility	Negative
Mycoplasma	Negative
Mycobacterium	Negative
TEM	Negative
PERT	Negative
In vitro assay for viral contaminants (MRC-5, Vero and Hela Cell line)	Negative
In vivo assay for viral contaminants	Negative
Human viruses (PCR)	
- CMV	Negative
- HAV	Negative
- HBV	Negative
- HCV	Negative
- Papilloma	Negative
- Polyoma	Negative
- HIV-1&2	Negative
- EBV	Negative
In vitro assay for porcine viruses	Negative
Extended assay for bovine viruses	Negative
Bovine viruses (PCR)	
- Polyoma	Negative
- Papilloma	Negative





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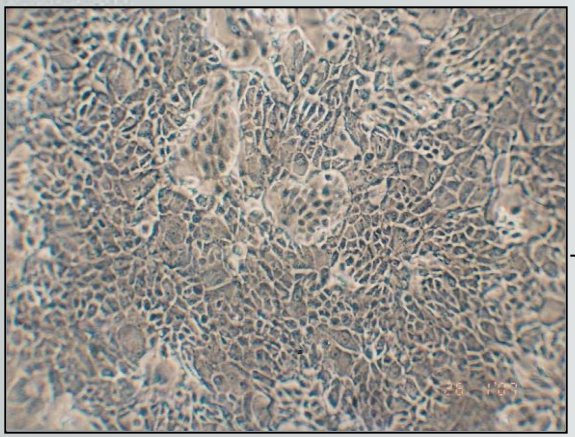
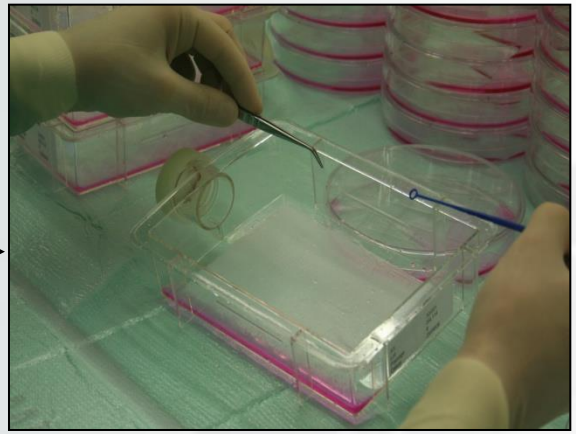
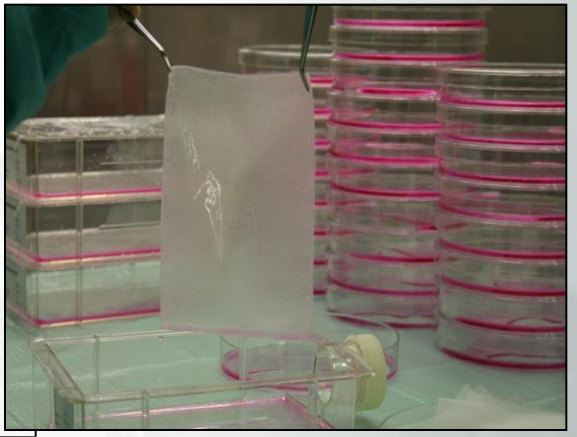
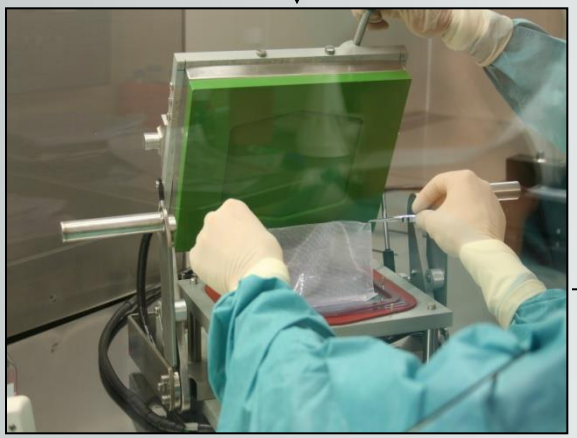
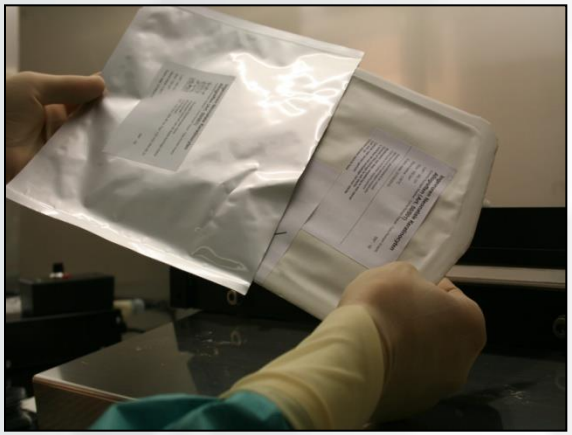
Donor Keratinocytes


QA/QC/RA Manager - Senior Scientist (Biologist)
Certification - Industrial Pharmacist
Final Release - Medical Director

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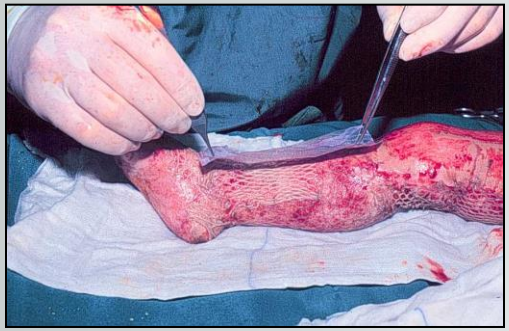
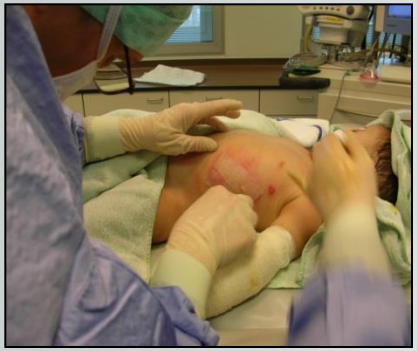
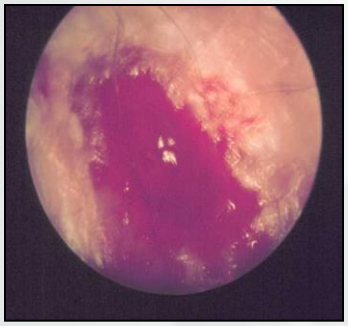
Indications for Use

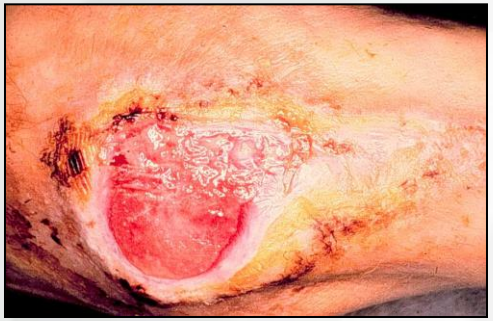




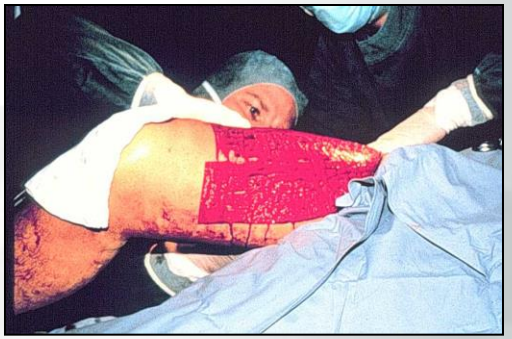
Burns



Chronic Ottorhea



Diabetic Ulcers



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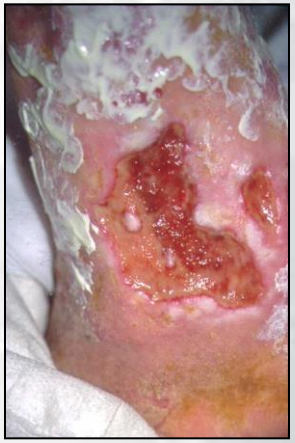

Venous Ulcers

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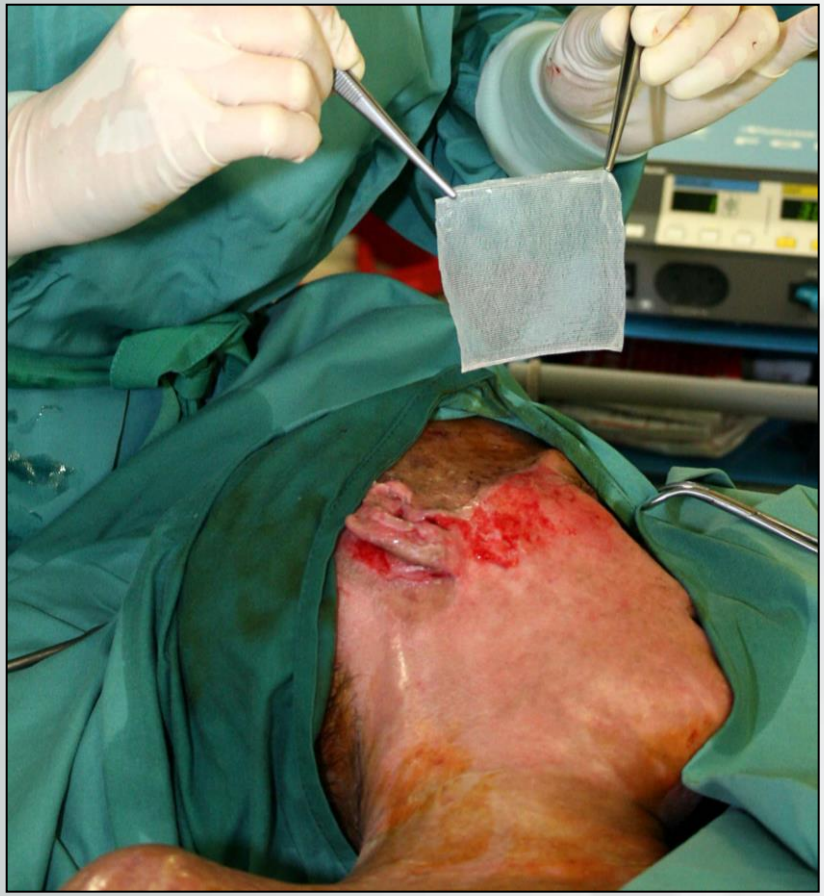
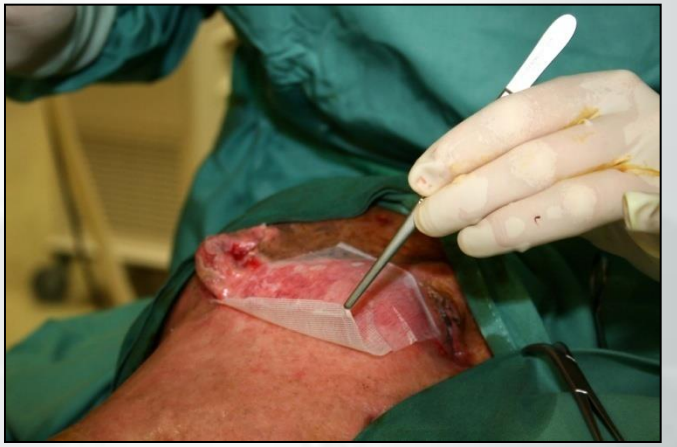
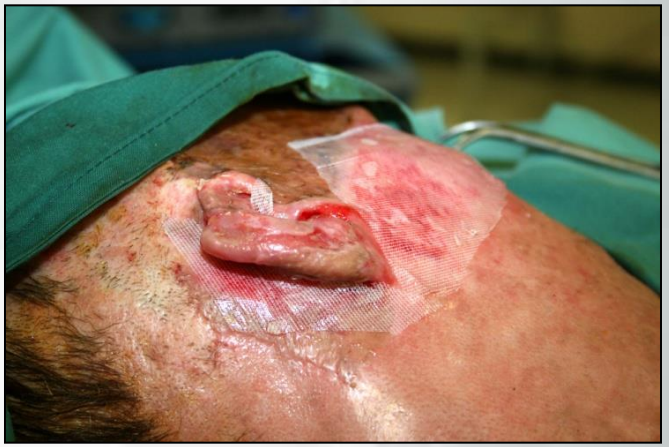
Keratinocyte Application







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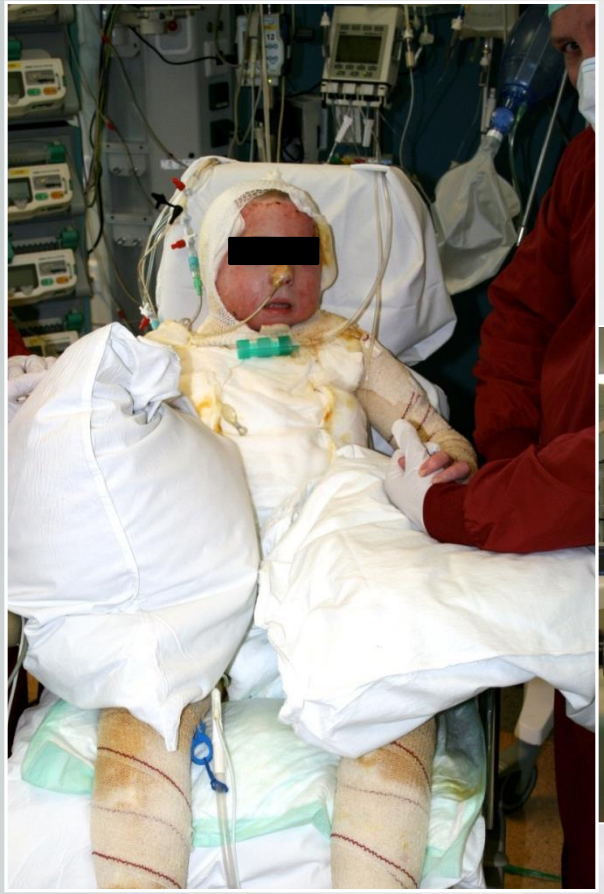
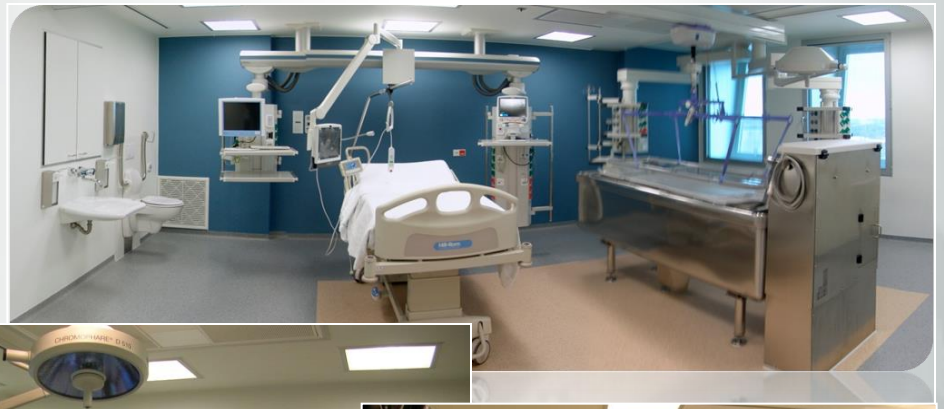
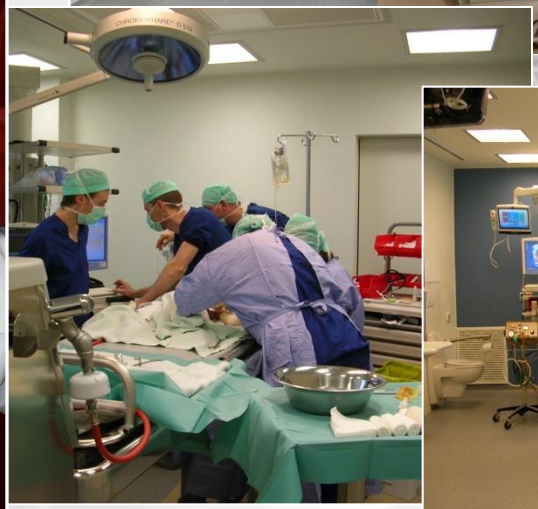
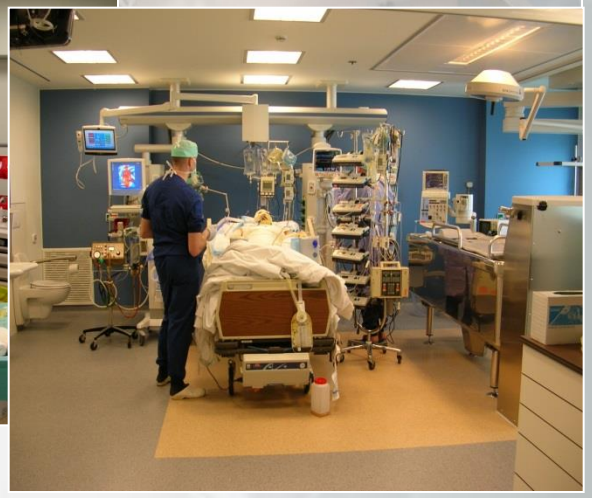
Patient, 9 Years, TBSA 95%









Cell Tissue Bank (2012) 13:175–189
DOI 10.1007/s10561-011-9247-3

Feeder layer- and animal product-free culture of neonatal foreskin keratinocytes: improved performance, usability, quality and safety

Peter De Corte · Gunther Verween · Gilbert Verbeken · Thomas Rose · Serge Jennes · Arlette De Coninck · Diane Roseeuw · Alain Vanderkelen · Eric Kets · David Haddow · Jean-Paul Pirnay

Received: 17 August 2010 / Accepted: 23 December 2010 / Published online: 11 March 2011

Cell Tissue Bank March 2012

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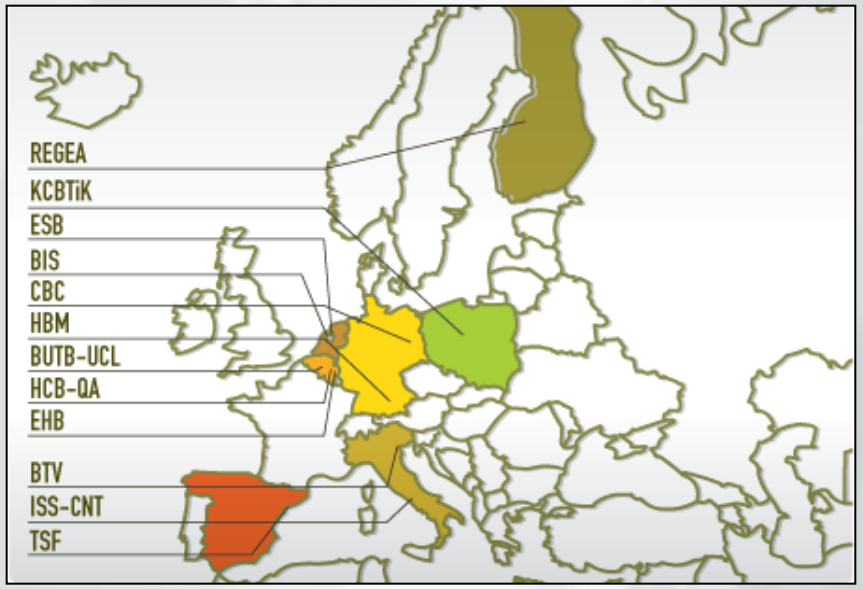
EuroGTPs

GENERAL OBJECTIVES:

- **To Develop Detailed European Good Tissue Practices for the Activities Carried Out in Tissue Establishments (TEs), Contributing to the Harmonization of these Activities Among European TEs in Order to Ensure a High Level of Quality and Safety of Tissue Grafts for Transplant.**
- **To Develop a Training Model for TE Personnel Based on the GTPs.**

http://eurogtps.com/



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Human Body Material (Human Cell- & Tissue Engineering)

- ***1970s*** *> Hospital Based / "Clinical Trials" / Tailor-Made Therapeutic Use*
  > Responsibility of the M.D. Supplier / - User

- ***1990s*** *> National Legal Frames*
  > (Non-Profit) Hospital Based Cell- and Tissue Banks
  > Hospital Inspection (DG 1)
  > Guidelines Public Health / Superior Health Council
  > Reimbursement by National Social Security Systems

- ***2010s*** *> European Cell- and Tissue Directives (Nat. Translations / Patchwork)*
  > Tissue Establishments / Hospital vs. Industry / Non-Profit vs. Profit
  > ATMP Regulation / Industrial Lobbying (Publ. 2007 > Impl. Dec. 2012)
  > Cherry-Picking
  > Cost-Increase / GMP / Pharmaceutical Products
  > Pharmaceutical Inspection (DG 3)
  > Marketing Authorization / Market Placement
  > Hospital Exemption
  > Ethical Aspects

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(Todays) "ATMPs"

- Medicinal Products
- Market Placement
- Market Authorization
- Hospital Exemption

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Business Model

- Uniform product development
- Uniform market placement
- Full blown GMP Production
- (IP Protection)
- Venture Capital
- Stock-market quotation
- Shareholders
- Return on investment

- "Business model"
- Operational (also treating patients?)
- Supported by competent authorities
- Increasing final product cost
- Increasing quality and safety (?)

(Non-Profit) Hospital Environment

- How to cope with the financial aspects and timelines linked to the pharma-pathway?
- Is this (uniform) approach relevant to (natural) phage therapy?
- Will quality and safety effectively increase?
- What social security system will be able to pay for these extra costs?

- PHAGE THERAPY is a THERAPEUTIC CONCEPT
- The EVOLUTIONARY BACTERIAL-PHAGE DYNAMICS can only be put to full advantage in therapy WHEN USING A TIMELY AND FLEXIBLE APPROACH

Biological Medicinal Products

Final product and treatment cost (*):

Cost for bringing biological medicinal products to the market is higher than the cost of putting classical (small chemical molecule) drugs into the market ...

- **Product development cost: App. 50-100.10^6 USD**
- **Timeline for development: +/- 8 years**
- **(Small molecule) chemical drug treatment: 2 USD / Day**
- **Treatment with biological (biosimilar) medicinal product: 55 USD / Day**

(*) Fleming Europe / Biosimilars MasterClass Training / 8-9 Feb. 2011 / Prague

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Reflections

- **GMP Produced (and Marketed) ATMPs Actually 10x More Expensive to Social Security System Than Similar Products Produced and Distributed Through (Non-Profit)Cells- & Tissue Directive Product Frame**

- **Only two ATMPs Cell Product on the European Market Today While ATMP Regulation Published in 2007**

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Regulator Thinking

Today's key paradigm:

" The precautionary principal "

Meaning:

" The complete evidence of risk *does not have to exist* to institute measures to protect individuals and society from that risk "

Regulator Thinking

What it should be:

" Balancing the risk avoidance principles with the broader risks to the community that CAN result from overzealous or inappropriate application of regulatory standards " *(Kirkland, 2010)*

E.g.:

Consider the Access to Lifesaving Therapies with a Certain Risk of Disease Transmission …

Application of legislation has to be flexible, adaptable and subject to review

World Health Organization

What does the Concept "Quality and Safety" Really Mean?

' a quality health service is one which organizes resources in the most effective way to meet the health of those most in need, for prevention and care, safely, without waste and within higher level requirements '

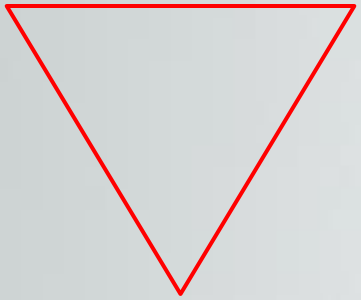
Pirnay et al, Cell Tissue Bank (2012) 13:487-498

- ***"Quality"*** **is not identical to "*Safety*"**
- ***"Efficacy"*** **may not be sacrificed in the name of quality and safety**
- **Product must be of high quality and safe in a sense of "*achieving the intended clinical utility*"**

"Patient Central"

Patient

Hospital



Microbiol. Lab

- Isolation
- Identification

- Phage production (outsourced or not)

  and / or

- Obtain phages through validated therapeutic phage libraries

---

- GMP production environment
- Phage-specific Q & S guidelines

Phage-Specific Q&S "Guidelines"

- To be developed at the European Level (experts' input included)
- Analogous to the historical development of the European "Human Cell- and Tissue Directives" ("Human Body Material Directive")

Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

Directive 20XX/XX/EC of the European Parliament and of the Council of XX XXXXX 20XX on setting standards of quality and safety for the procurement, testing, processing, preservation, storage and distribution of natural bacteriophages for human use

Pharm Res
DOI 10.1007/s11095-014-1617-7

PERSPECTIVE

Quality and Safety Requirements for Sustainable Phage Therapy Products

Jean-Paul Pirnay • Bob G. Blasdel • Laurent Bretaudeau • Angus Buckling • Nina Chanishvili • Jason R. Clark • Sofia Corte-Real • Laurent Debarbieux • Alain Dublanchet • Daniel De Vos • Jérôme Gabard • Miguel Garcia • Marina Goderdzishvili • Andrzej Górski • John Hardcastle • Isabelle Huys • Elizabeth Kutter • Rob Lavigne • Maia Merabishvili • Ewa Olchawa • Kaarle J. Parikka • Olivier Patey • Flavie Pouilot • Gregory Resch • Christine Rohde • Jacques Scheres • Mikael Skurnik • Mario Vaneechoutte • Luc Van Parys • Gilbert Verbeken • Martin Zizi • Guy Van den Eede

Received: 2 December 2014 / Accepted: 30 December 2014

Pharm Res December 2014

(Non-Profit) Lobbying

At the level of:

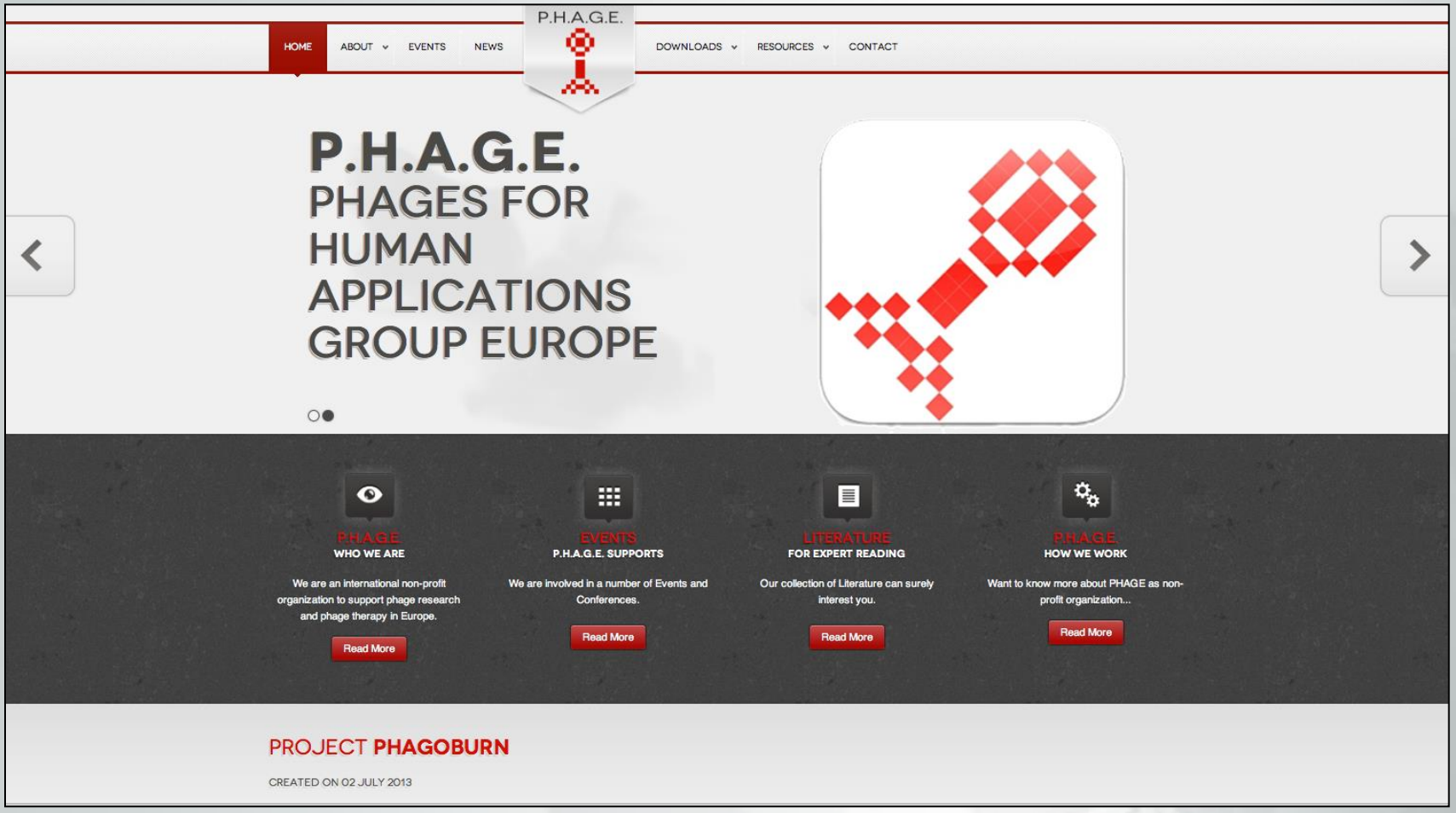
- **The European Parliament**
- **The European Commission**

Asking for a dedicated European "Phage Directive" that guarantees quality and safety, (NEXT TO ?) the actual Medicinal Products Legal Frames

Through:

- **Different Members States**
- **Different Patient Organizations**
- **Different MDs ("applying" or "wanting to apply" natural therapeutic bacteriophages)**

P.H.A.G.E.org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Read More
PROJECT PHAGOBURN
CREATED ON 02 JULY 2013

Legal Vacuum

Lawyers Office BREDIN PRAT (Paris / Brussels):

Scope of the Medicinal Product Directive 2001/83/EC (Title II / Article 2 / Par 1):

The Directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process

Reflexion:

Are hospitals that are producing their own grafts for use on their own patients, based on a individual prescription, inside their own hospital, without losing control over the final product, covered by the scope of the medicinal product directive? Do they perform market placement? When not ...

- **Directive 2001/83/EC not relevant to these hospitals ...**

Demonstrating Efficacy

PhagoBurn

- Multicentre, Multinational Clinical Trial (FRA, BEL, SUI)
- *Escherichia coli* and *Pseudomonas aeruginosa*
- 5 Million EUR (EC 3.8 millions EUR)
- Launched June 1th 2013

Ethics

Hindawi Publishing Corporation
BioMed Research International
Volume 2014, Article ID 621316, 8 pages
http://dx.doi.org/10.1155/2014/621316

Hindawi

Research Article

Taking Bacteriophage Therapy Seriously: A Moral Argument

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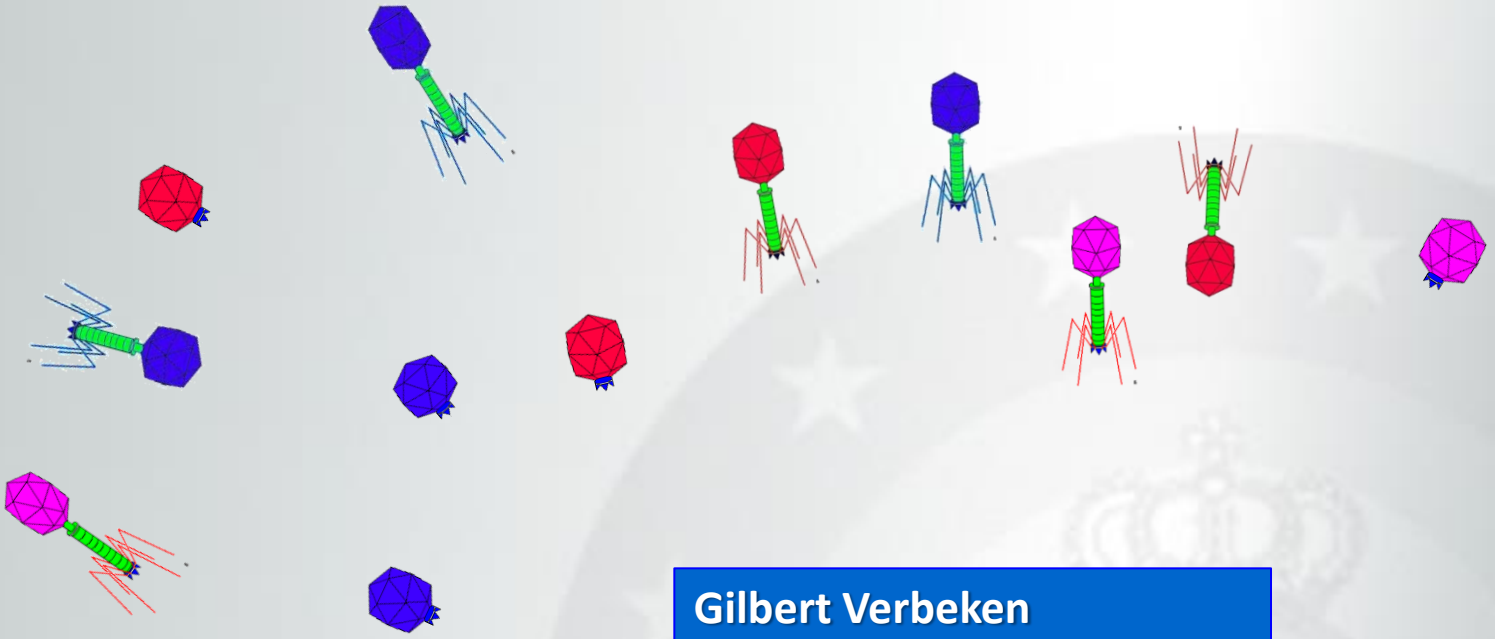
Thanks



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